

Study on Prevalence of Microalbuminuria in newly diagnosed non-Diabetic essential Hypertension Patients in tertiary care Hospitals in South India

Jayamohan Kokkat¹, Anoop Many², Sandheep George Villoth³

¹Associate Professor, Department of General Medicine, Sree Narayana Institute of Medical Sciences, Chalakka North Kuthiyathode, Ernakulam District, Kerala- 683594, India.

²Consultant Physician, General Hospital, Adoor, Pathanamthitta District, Kerala-691523, India.

³Consultant Cardiologist, St. Mary's Hospital Thodupuzha, Idukki District, Kerala-685584, India.

Email: jayamohankokkat@gmail.com

DOI: 10.47750/pnr.2022.13.501.84

Abstract

Background: Hypertension affects about one billion individuals worldwide. The prevalence of hypertension has increased over the past decade, reaching an alarming level of 25% among the general population in the United States and an even higher percentage in Europe. It is an established risk factor for the development of cerebral, cardiac, and renal events. Microalbuminuria, defined as urine albumin excretion of 30 - 300mg/L of 24 hrs urine or 20 - 200 mg/min in a random or timed urine sample is now considered as an early marker of progressive renal damage and also an independent risk factor for Cardio vascular disease (CAD). The present study was conducted in order to test the usefulness of estimating microalbuminuria in non-diabetic essential hypertension patients as early as at the time of diagnosis of hypertension. **Materials and Methods:** This is cross sectional study. The study was conducted during the period May 2018 to July 2019 in the Department of General Medicine, Tertiary Care Hospitals in South India. **Results:** The percentage of normal, high normal and microalbuminuria in the control group are 36%, 52% and 12% respectively while that in hypertension group is 12%, 42% and 46% respectively. There was a significant positive correlation between prevalence of microalbuminuria and blood pressure values, both systolic and diastolic blood pressure. **Conclusion:** Microalbuminuria, a marker of CVD and Chronic Kidney Disease (CKD) burden, is a useful non- invasive screening tool in identifying the hypertensive patients with a high risk of developing cardiac and renal complications.

Keywords: Hypertension, Microalbuminuria, Cardio vascular disease and Chronic Kidney Disease.

1. INTRODUCTION

Hypertension is reported to be the seventh highest contributor to premature death in developing countries 1. It has been estimated that hypertension accounts for 6% of deaths worldwide. Earlier reports also suggest that prevalence of hypertension is rapidly increasing in developing countries and is one of the leading causes of death and disability in developing countries. Recent reports indicate that nearly 1 billion adults (more than a quarter of the world population) had hypertension in 2000, and this is predicted to increase to 1.56 billion by 20252.

Essential hypertension remains a major modifiable risk factor for cardiovascular disease (CVD) despite important advances in our understanding of its pathophysiology and the availability of effective treatment strategies. There is established evidence that effective treatment of hypertension is associated with a significant reduction of cardiovascular events, yet the number of patients who are aware of their condition and who achieve adequate BP control remains unacceptably low3.

In the past decade, the incidence of end-stage renal disease, the prevalence of heart failure and age-adjusted rates of stroke incidence have increased. A major contributor to these trends is inadequate control of BP in the hypertensive population. In spite of the dreaded complications associated with uncontrolled hypertension, the disease remains inadequately treated in most patients, mainly due to its insidious onset and asymptomatic nature even as it progressively damages multiple organ systems. Therefore many people with essential hypertension may present with overt or sub-clinical organ damage involving the heart,

kidneys, central nervous system or retina at the time of initial diagnosis. . HTN has become a major public health problem that needs to be faced with more aggressive treatment strategies to contain the incumbent epidemic of cardiovascular complications. The main issue at this context is to identify the target or sub group that is at higher risk for future events⁴.

The goals of initial evaluation of a hypertensive patient are to determine baseline BP; assess the presence and extent of target organ damage and concomitant CVD; screen for potentially curable specific causes of hypertension (secondary hypertension); identify hypertensinogenic factors (obesity, insulin resistance, high alcohol intake, high salt intake, a sedentary lifestyle, stress, dyslipidemia, and low potassium or calcium intake) and other CVD risk factors; and characterize the patient to facilitate the choice of therapy (especially drug selection) and define prognosis.

Cardiovascular and renal complications of hypertension remain high compared to central nervous system or ophthalmological complications. Renal dysfunction by itself is independently associated with an increased risk for cardiovascular events (CVEs)⁴. It has also been pointed out that the cardiovascular risk progressively increases as renal function declines. Therefore identifying the precursors of overt kidney disease is of utmost importance to limit the burden of cardiovascular and renal morbidity and mortality in hypertensive patients. European guidelines for hypertension⁵ emphasize the importance of assessing the presence of organ damage for cardiovascular risk stratification. Noninvasive assessment of cardiac and peripheral arterial structures by ultrasonography resulted in correctly identifying a greater number of high-risk patients. This could have important prognostic and therapeutic implications. Unfortunately, because of its relatively high cost, this procedure is not yet performed routinely, and guidelines still recommends ultrasonography only in selected cases. On the other hand a restrictive diagnostic approach to risk stratification could lead to significant misclassification of patients and underestimation of their actual absolute risk⁶.

Microalbuminuria, defined as urine albumin excretion of 30 - 300gm/L of 24 hrs urine or 20 - 200 mg/min in a random or timed urine sample is now considered as an early marker of progressive renal damage and also an independant risk factor for CVD. A strong association exists between microalbuminuria and signs of subclinical organ damage, such as left ventricular hypertrophy (especially concentric geometry), and increased carotid wall thickness ⁶. Recently, interest in the study of microalbuminuria has grown because it may represent a useful non-invasive and relatively inexpensive clinical tool for the identification of hypertensive patients at higher risk for cardiovascular and renal damage. Several epidemiological studies show an association between microalbuminuria and increased morbidity and mortality especially that caused by cardiovascular disease independently of other risk factors. Increased urinary albumin excretion (UAE) related to unfavorable cardiovascular outcomes in patients with diabetes and in high-risk patients has been investigated in several landmark trials. However there is less information about the association of microalbuminuria in nondiabetic hypertensives belonging to the South Indian population and also as early as at the time of diagnosis of hypertension.

Yet another powerful indicator of progressive kidney disease is the declining glomerular filtration rate (GFR). Assessment of kidney function for target organ damage at the time of diagnosis of hypertension helps in identifying the high risk patients and thereby helps in appropriate treatment selection. Microalbuminuria and GFR are valuable parameters in identifying target organ damage at an early stage. With early detection, however, the cardiovascular risk can be reduced and the onset of kidney disease can be slowed, halted, and in some cases reversed through treatment with drugs such as inhibitors of angiotensin-converting enzyme (ACE) and angiotensin-2 receptor blockers (ARB) ⁷. Thus, it is an indicator of the need for more intensive efforts to reduce cardiovascular risk factors.

The present study aims to determine the prevalence of microalbuminuria in newly diagnosed non-diabetic essential hypertension patients belonging to the South Indian population. The microalbuminuria is also correlated with GFR at the time of diagnosis.

2. Materials and Methods

This is a cross sectional study and conducted during the period 2018 to July 2019 in the Department of General Medicine, Tertiary Care Hospitals in South India. 50 newly diagnosed essential hypertension patients without diabetes mellitus / family history of diabetes mellitus attending the Medicine Out Patient Department were enrolled in the study after getting an informed consent. The patients belonged to different socioeconomic and religious backgrounds. The study parameters were estimated in the patients and compared with 50 age and sex matched healthy controls without hypertension and without diabetes mellitus.

Ethical clearance was obtained from Institutional Ethical Committee before collection of the samples.

2a. Diagnosis of Hypertension

After a rest of 15 min, the BP of each participant was measured, using the auscultatory method with a standardized calibrated mercury column-type sphygmomanometer with an appropriate-sized cuff encircling at least 80% of the arm in the seated posture, with feet on the floor and arm supported at heart level. The first appearance of sound (phase 1) is used to define SBP. The disappearance of sound (phase 5) is used to define DBP. Two separate measurements were recorded at five-minute intervals and the average of the two values was taken as the BP at that moment. Similar BP measurements were done on three occasions, a week apart, and a BP above 120/80 mm Hg was the inclusion criterion. Secondary causes of hypertension were ruled out by a detailed history taking and routine radiological investigations. The enrolled subjects were then grouped into two.

Group A - controls (SBP < 120mmHg / DBP < 80mmHg) and

Group B - hypertension patients (SBP \geq 140mmHg / DBP \geq 90mmHg)

2b. Biochemical analysis

Microalbumin was analyzed by turbidimetric method is used for quantitative estimation of microalbumin in urine. Urine creatinine was estimated by the method of Alkaline Picrate. All the kits were purchased from sigma chemicals remaining chemicals purchased from SRL chemicals, Chennai.

2c. Urine parameters

Participants were given a sterile plastic container with lid and were instructed to collect a first-void early-morning urine sample on the day of interview, to be used for albumin and creatinine estimation. Urine samples were refrigerated at 4°C within 3 hrs of arrival at the laboratory. The urine albumin is stable for up to 7 days when refrigerated at 4°C. The samples were analyzed within three or four days.

However, it is acknowledged that estimation of urinary protein excretion over a 24- h period is the reference or gold standard method. The need for a 24-h collection is a result of the high degree of variation in the urinary protein concentration during the course of the day. This approach, is considered by many to be impractical in some circumstances, particularly in the outpatient setting, because of the difficulties associated with obtaining a complete collection.

Urine albumin excretion varies with exercise, posture, fever and asymptomatic bacteriuria. This precludes the use of a shorter collection period or the use of a random urine sample for protein concentration measurements, the latter of which would be the most practicable. Since urine creatinine concentration is fairly constant throughout the day, measurement of protein / creatinine ratio (PCR) or albumin / creatinine ratio (ACR) allows correction for variations in urine protein concentration in an early morning first void or second void urine and random urine.

3. Results

Age wise case Distribution

The controls and the hypertensive subjects were all between 30 and 60 years of age. The age distribution in three ranges namely, 31-40, 41-50 and 51-60 in the control group and hypertension group is given in Table 1.

1. Age wise Case Distribution

Table 1

Age group (yrs)	Control group	Hypertension group
31 - 40	19	17
41 - 50	16	14
51 - 60	15	19
Total	50	50

Baseline characteristics of the study population

The baseline characteristics of the two study groups with the mean, SD and p value are given in Table 2. The systolic and diastolic blood pressure values of hypertension patients is significantly higher (p value <0.001) than that of control group.

The total cholesterol values and LDL-cholesterol values of hypertension group are also significantly greater (p values 0.046 and 0.040 respectively) than that in control group.

The mean value for urine microalbumin and ACR is higher in hypertensive group compared to control group as shown in Table 2. The p value <0.001 is statistically significant. Also the eGFR of hypertension group is significantly lower (p value <0.001) than that of control group.

Table 2: baseline characteristics

Gender/groups	Control group	Hypertensive group
Male	29	29
Female	21	21
Total	50	50

Prevalence of microalbuminuria

The prevalence of microalbuminuria was studied in three groups namely normal albuminuria (<10mg/gm in males, <15 mg/gm in females), high normal albuminuria (10-19 mg/gm in males, 15-29 mg/gm in females) and microalbuminuria (20-200 mg/gm in males, 30-300 mg/gm in females) Out of 50 hypertension patients 23 had microalbuminuria while in the control group only 6 had microalbuminuria. The percentage prevalence of albuminuria in normal, high normal and microalbuminuria levels in the control group and hypertension group is shown as a pie chart in Chart 1 and 2 respectively.

Figure -1: Microalbuminuria control group

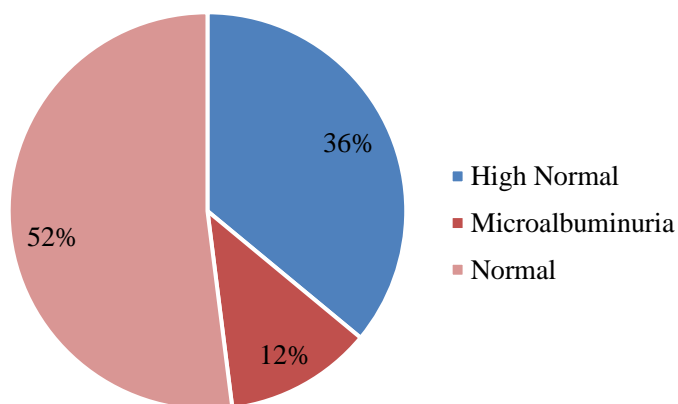
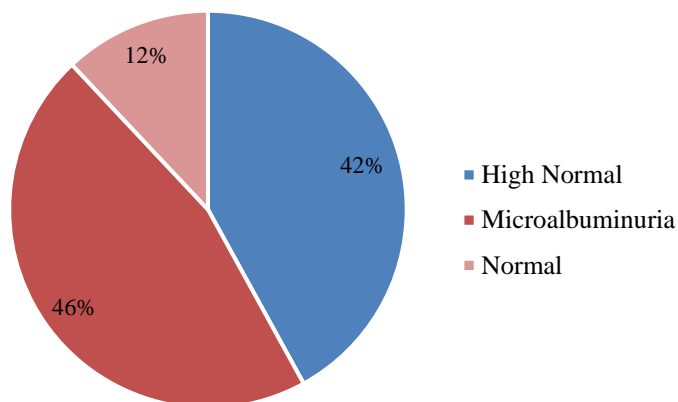
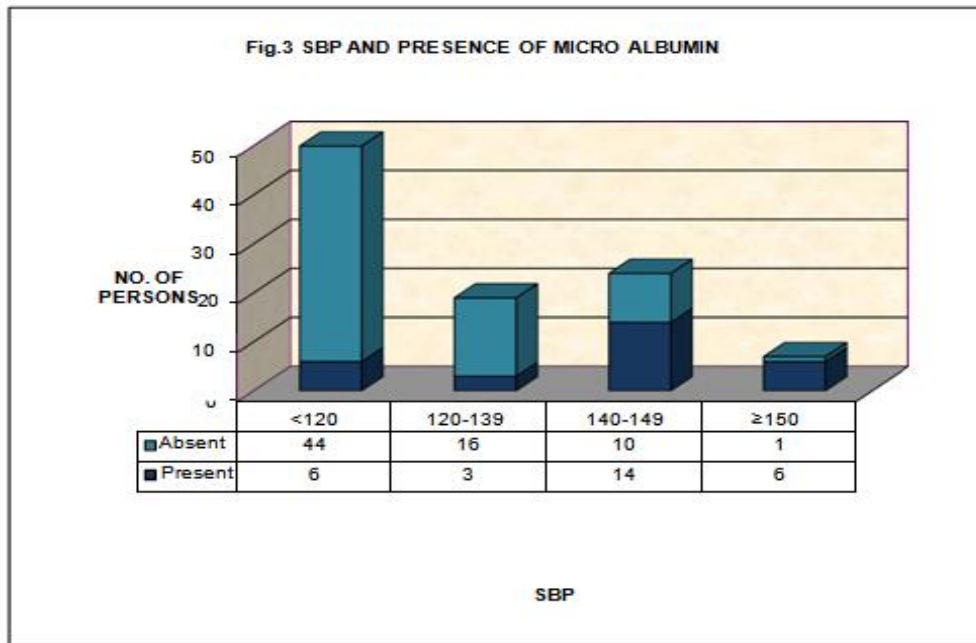


Figure 2. Microalbuminuria in Hypertensive Group



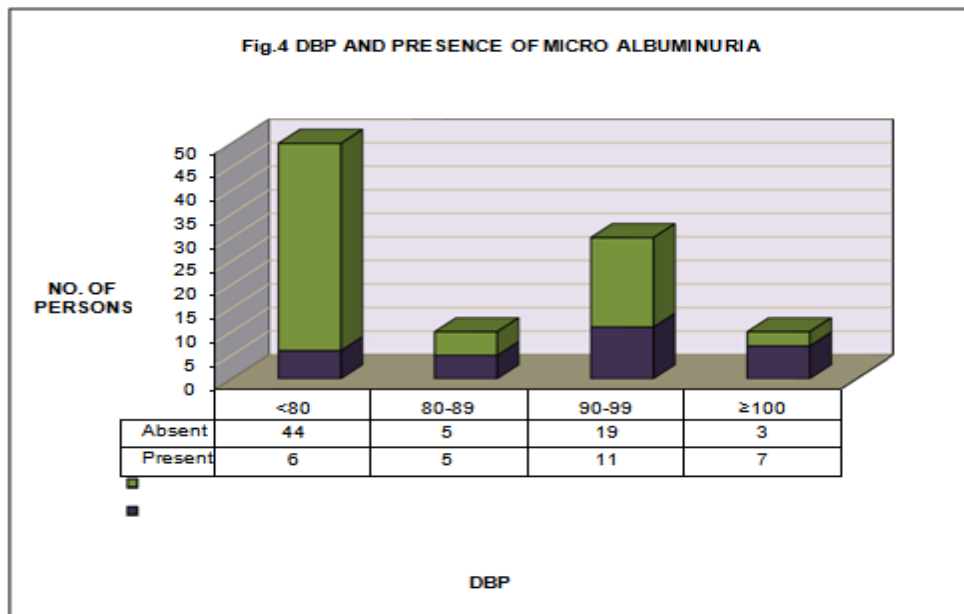
Distribution of Microalbuminuria at Various Levels of Systolic Blood Pressure

Microalbuminuria present at four levels of systolic blood pressure (SBP) namely <120 mmHg, 120-139mmHg, 140-149 mmHg and \geq 150 mmHg is shown in above chart. All subjects in the control group fall in <120 category. There was a significant association between prevalence of microalbuminuria with increasing levels of SBP.(Fig.3)



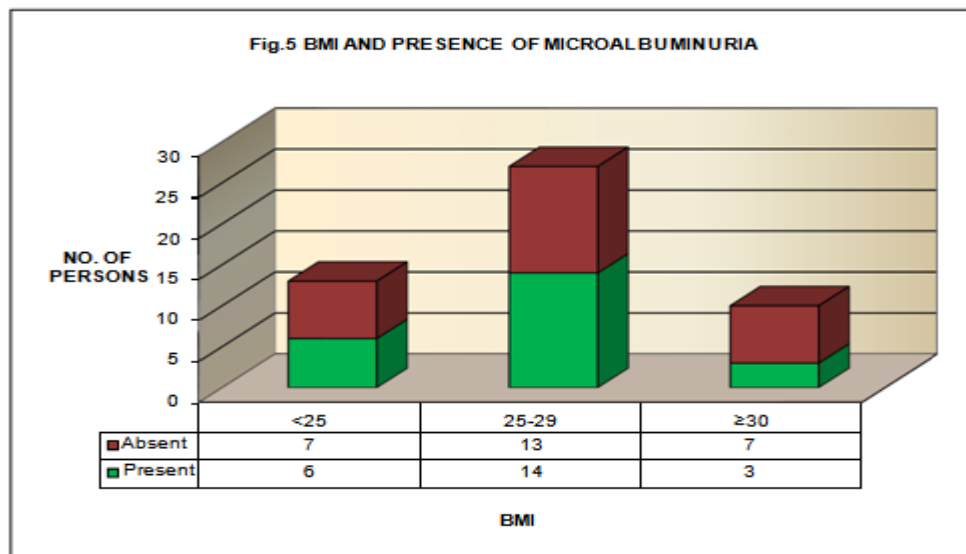
Distribution of Microalbuminuria at Various Levels of Diastolic Blood Pressure

In the hypertension group, microalbuminuria was present in 5 out of 10 individuals in 80-89 mmHg group of diastolic blood pressure (DBP), 11 out of 30 in 90-99 group and in 7 out of 10 in ≥ 100 group. All the controls belonged to < 80 group and microalbuminuria was present in 6 out of 50 individuals. The prevalence of microalbuminuria at various levels of DBP was statistically significant. (Fig.4)



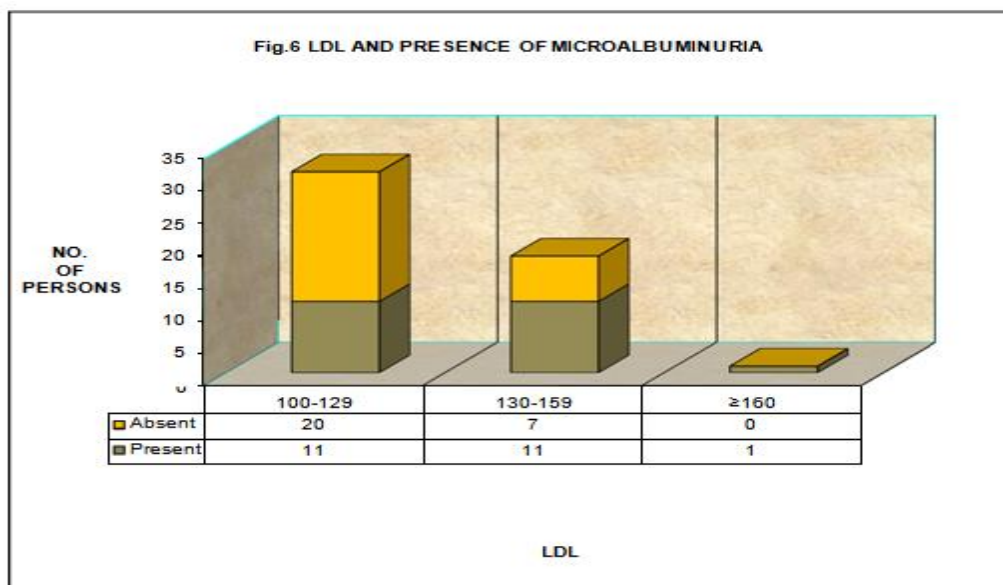
BMI and Microalbuminuria

In the hypertension group, the presence or absence of microalbuminuria at three levels of BMI, namely < 25 , 25-29.9 and 30-34.9 is shown in the above chart. Microalbuminuria was present in 46% of individuals with BMI < 25 , in 52% of individuals with BMI 25-29.9 and in 30% of individuals with BMI 30-34.9. (Fig.5)



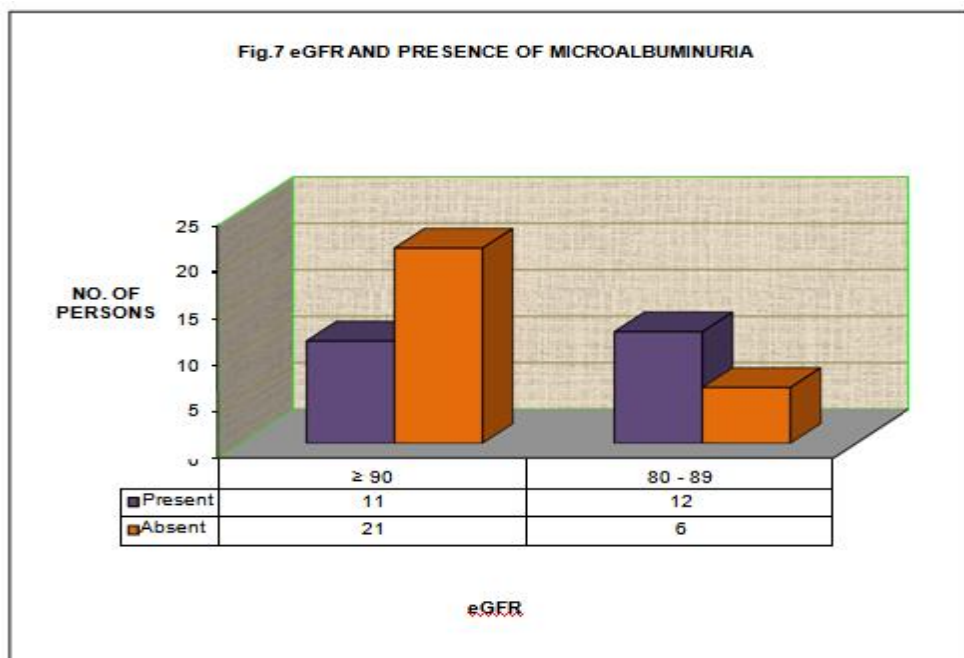
LDL Cholesterol and Microalbuminuria

The hypertension group was categorised into three based on their LDL values as 100 - 129, 130-159 and ≥ 160 . There was only one individual with LDL value ≥ 160 and was positive for microalbuminuria. In 100-129 group, 11 out of 31 individuals had microalbuminuria while in 130-159 group, 11 out of 18 had microalbuminuria as shown in above chart. The LDL values had significant positive correlation with prevalence of microalbuminuria. (Fig.6.)



eGFR and Microalbuminuria

Comparison of eGFR values with the presence or absence of microalbuminuria in the hypertension group is shown in the above chart, in which 34% of individuals with microalbuminuria had eGFR ≥ 90 ml/min while 67% of individuals with microalbuminuria had eGFR between 80-89 ml/min. There was a significant negative correlation between eGFR and prevalence of microalbuminuria. (Fig.7)



4. Discussion

Hypertension is a major public health problem all over the world. The incidence of hypertension in India is 5 to 15% compared to 10 to 12% in the West.

In the present study urine microalbumin was estimated in the newly diagnosed essential hypertension patients without diabetes in order to identify early target organ damage. This study tests the usefulness of urine microalbumin as a screening tool for identifying target organ damage as early as at the time of diagnosis.

The results obtained were statistically analysed by SPSS (Statistical package for Social Science) software V.16.0 and by Graph Pad Prism software.

Prevalence of Microalbuminuria

In the present study microalbuminuria was significantly higher in hypertensive patients compared to controls. (p value 0.007). The prevalence of microalbuminuria in this study was 46% (23 patients out of 50). In 1991 Stefano Bianchi et al published the first large study on microalbuminuria in hypertensives and were found to be 35%.

In 2002, a study by Tsioufis et al reported a prevalence of 47% and in 2008, Hitha B et al⁸ reported a prevalence of 26.6%. Summerson et al⁹ found a 32% prevalence in group of black hypertensive patients while Bigazzi et al¹⁰ reported a high prevalence of microalbuminuria of 40% in a group of 123 unselected patients with essential hypertension.

Pontremoli et al¹¹ reported 6.7% prevalence of microalbuminuria in untreated patients with mild to moderate essential hypertension. This figure differs from those of several previously published reports that indicate a variable but considerably higher prevalence of microalbuminuria.

Age and Sex distribution of Microalbuminuria

In the present study the mean microalbumin excretion in the three age groups 31-40, 41-50 and 51-60 yrs were 23, 28.1 and 28.9 respectively. Though the mean was higher in higher age groups it was not statistically significant (p value > 0.05). Campese

Vito M et al¹² and Hitha B et al⁸ showed an increase in prevalence of microalbuminuria with increasing age.

The prevalence of microalbuminuria was higher in men was 48% (14 out of 29) while that in women was 43% (9 out of 21). The difference was not statistically significant (p value >0.05).

Campese Vito M et al¹² showed a prevalence of 32% in males and 28% in females. In the HUNT study (Nord Trondelag Health Study, Norway) a stronger association was observed between microalbuminuria and mortality in men than in women. Pontremoli et al¹¹ also showed an increased prevalence of microalbuminuria in men compared to women. In an Indian study by Todkar et al¹³ there was a higher prevalence of microalbuminuria in females compared to males.

Blood pressure and microalbuminuria

There was a significant increase in the prevalence of microalbuminuria with increase in SBP (p value 0.004) as seen in Chart 5.5.

Among the 50 hypertensive patients microalbuminuria was present in 11 out of 18 with SBP 120-139 mmHg, 7 out of 17 with 140-149 mmHg, 9 out of 14 with 150-159 mmHg which was statistically significant.

The DBP also had a significant positive correlation with microalbuminuria (p value 0.0168). Microalbuminuria was present in 6 out of 10 with DBP 80-89 mmHg, 14 out of 30 patients with 90-99 mmHg and 7 out of 10 patients with ≥ 100 mmHg which was statistically significant.

In a study by M Mettmano et al¹⁴ no significant correlation between microalbuminuria and clinic systolic and diastolic blood pressure were observed, but a strong relation between 24hr blood pressure and urine albumin excretion was reported. In the MAGIC study the prevalence of microalbuminuria correlated significantly with the height of BP when considering office measurements and more so in 24hr ambulatory BP monitoring¹⁵.

BMI and Microalbuminuria

Mean BMI in the patients with microalbuminuria (30.3) was higher than those without microalbuminuria (29.3) but not statistically significant (p value 0.641). There was a non- linear association of microalbuminuria at all the three levels of BMI (<25, 25-30, 30-34).

A study by Maria Ferris et al¹⁶ in 2007 supports a strong association between morbid obesity and the presence of albuminuria in young adults, but not with BMI <35. As morbid obesity was an exclusion criterion in the present study, a significant association between microalbuminuria and BMI was not obtained. But, in a study by Martin Thoenes et al¹⁷ there was a significant increase in the prevalence of microalbuminuria in the three levels of BMI (<25, 25-30, >30).

LDL and Microalbuminuria

The data from the present study reports a statistically significant difference in the prevalence of microalbuminuria with respect to total cholesterol (p value 0.046) and LDL levels (p value 0.040) in the hypertension group.

Microalbuminuria was present in 14 out of 31 patients with LDL 100-129 mg/dl, 14 out of 18 with 130-159 mg/dl and in 1 out of 1 patient with ≥ 160 mg/dl. There was no significant association between HDL cholesterol and microalbuminuria.

In the Gubbio study¹⁸, microalbuminuria was associated with high LDL and low HDL which are an unfavourable lipid profile and are established risk factors for CVD. In one study by B Hitha et al⁸ microalbuminuria was significantly higher in patients with unfavourable lipid profile compared to patients with favourable lipid profile.

eGFR and Microalbuminuria

There was a significant negative correlation between eGFR and prevalence of microalbuminuria (p value < 0.001) as seen in

Chart 5.9. Based on the eGFR the patients were grouped as eGFR 60-89 ml/min and eGFR ≥ 90 ml/min. Microalbuminuria was present in 13 out of 18 patients in group 60-89 and 14 out of 32 patients in group ≥ 90 which was statistically significant and also the mean microalbumin in group 60-89 (33.4) was significantly higher than that in group ≥ 90 (22.8).

Verhave et al.¹⁹ studied 6022 individuals who were from the general population and had eGFR >60 ml/min per 1.73m² and found that increasing albumin excretion, even in the normal range, was associated with increasing risk for renal function loss. At the same level of eGFR, the risk rises substantially when micro- or macroalbuminuria is present.

Another study by Hallan et al.²⁰ concludes that eGFR and ACR complement each other very well, leading to a strong prediction of CKD and ESRD. Roughly, ACR is a marker of the rate of progression, whereas eGFR is a marker of how advanced the disease process is.

5. Conclusion

In the Presence study we conclude that the Microalbuminuria as a marker of CVD and CKD burden, is a useful non-invasive screening tool in identifying the hypertensive patients with a high risk of developing cardiac and renal complications.

REFERENCES

1. Wolf-Maier K, Cooper RS, Banegas JR, Giampaoli S, Hense HW, Joffres M, Kastarinen M, Poulter N, Primatesta P, Rodriguez-Artalejo F, Stegmayr B, Thamm M, Tuomilehto J, Vanuzzo D, Vescio F: Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA* 289: 2363–2369, 2003.
2. Messerli FH, Williams B, Ritz E. Essential hypertension. *Lancet* 2007; 370: 591-603.
3. Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR, Poulter N, Primatesta P, Stegmayr B, Thamm M: Hypertension treatment and control in five European countries, Canada, and the United States. *Hypertension* 43: 10–17, 2004
4. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY.: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296–1305, 2004.
5. Guidelines Committee: 2003 European Society of Hypertension-European Society of Cardiology. Guidelines for the management of arterial hypertension. *J Hypertens* 21: 1011– 1053, 2003.
6. Pontremoli R, Ravera M, Bezante GP, Viazzi F, Nicoletta C, Berruti V, Leoncini G, Del Sette M, Brunelli C, Tomolillo C, Deferrari G: Left ventricular geometry and function in patients with essential hypertension and microalbuminuria. *J Hypertens* 17: 993–1000, 1999.
7. Ibsen H, Wachtell K, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, Dahlöf B: Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: The LIFE Study. *Kidney Int Suppl* 92: S56–S58, 2004.
8. Teppo A.M. (1982). *Clin. Chem*; 28: 1359.
9. Bell J L., McNeill D. P.O., Dandona P., Wojdyla J.W. (1986). *Clin. Chem*; 32:1412
10. Sathianathan P., Rege V.P., Barron J.L. (1986). *Clin. Chem*; 32:202
11. Brod, J and Sirota, JH (1948). The Renal Clearance Of Endogenous "Creatinine" In Man. *Journal of Clinical Investigation*; 27: 645.
12. Buccolo G., David M., *Clin Chem.* 19, 476(1973)
13. Allain C.A., et al., *Clin Chem.* 20, 470.(1977)
14. Castelli W. P., et al, *Lancet* 1, 965(1977)
15. B Hitha, JM Pappachan, H Balachandran Pillai, P Sujathan. Microalbuminuria in Patients With Essential Hypertension And its Relationship to Target Organ Damage: An Indian Experience. *Saudi J Kidney Dis Transpl* 2008;19:411-9.
16. Summerson JH, Bell RA, Konen JC. Racial differences in the prevalence of microalbuminuria in hypertension. *Am J Kidney Dis.* 1995;26:577-579.
17. Bigazzi R, Bianchi S, Campese VM, Baldari G. Prevalence of microalbuminuria in a large population of patients with mild to moderate essential hypertension. *Nephron.* 1992; 61:94-97
18. Pontremoli R., Leoncini G., Ravera M., Parodi D., Tomolillo C. Microalbuminuria: cardiovascular and Renal Risk in Primary Hypertension. *J Am Soc Nephrol* 13: S(169-172); 2002.
19. Trioufis, C, Stefandis – microalbuminuria associated with unfavourable cardiac geometric adaptations in essential hypertension patients. *J of Hum Hyp* 2002;16:249-254
20. Campese Vito M, Roberto B., Stefano B., Georgio B. Prevalence Of Microalbuminuria In A Large Population Of Patients With Mild To Moderate Essential Hypertension. *Nephron* 1992;61:94-97.